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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,636	11/25/1997	ELAZAR RABBBANI	ENZ-53(DIV-3	4642
28171	7590	12/26/2007	EXAMINER	
ENZO BIOCHEM, INC. 527 MADISON AVENUE (9TH FLOOR) NEW YORK, NY 10022			BOWMAN, AMY HUDSON	
			ART UNIT	PAPER NUMBER
			1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

08/978,636

Applicant(s)

RABBBANI ET AL.

Examiner

Amy H. Bowman

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 October 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 245-255, 258, 262, 265, 268 and 269 is/are pending in the application.
- 4a) Of the above claim(s) 268 and 269 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 245-255, 258, 262, and 265 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 November 1997 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 10/9/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 4/4/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 245-255, 258, 262, 265, 268 and 269 are pending in the instant application.

This application contains claims 268 and 269 that are drawn to an invention nonelected with traverse in the reply filed on 10/9/07. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's arguments and/or amendments to the claims filed on 10/9/07 have been fully considered. However, the instant rejections are pending and upon further consideration of the instant amendments, a new rejection is applied as explained below.

Response to Applicants Arguments-- 35 USC § 112

Claims 245-255, 258, 262 and 265 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection

is repeated for the same reasons of record as set forth in the actions mailed 5/31/05, 6/27/06 and 4/4/07.

Applicant argues that the instant claims recite that the presence of the intron is responsible for lack of expression in a prokaryotic cell and therefore one would not use any intron. Applicant argues that the intron used would have to be responsible for lack of expression of the gene product in a prokaryotic cell. Applicant asserts that one of skill in the art would know which features are necessary in the intron in order to possess this function. Applicant explains that for example, the simple expedient of determining the number of nucleotides in the intron would generate a frame shift in the coding is an obvious approach which also indicates that 1/3 of the introns chosen at random would have this feature; the presence of stop codons is another easily ascertainable approach, and thus it would be evident to one of skill what characteristics in an intron would be appropriate to use the constructs of the invention.

However, it is important to note that the instant claims are not limited to the embodiments addressed by applicant above. The specification does not provide support for the use of any intron, in any polymerase or any bacteriophage polymerase, or any conditionally toxic gene, in any eukaryotic or prokaryotic cell because the specification provides only minimal description of any particular intron, polymerase (including bacteriophage polymerase), or toxic gene, or eukaryotic or prokaryotic cells for whom known structures exist that could be utilized having the claimed function.

The specification provides for the use of T3, T7 or SP6 polymerases, and also for the use of certain "consensus" splice donor and acceptor sites for inserting introns.

Applicants prophetically suggest that intron "insertion at any of these sites in a gene coding region should not affect subsequent removal of the processing element in a compatible cell." (page 84 of the instant specification). However, there is significant unpredictability in such intron removal, since such a process requires a complex interaction between the nucleic acid construct and the already existent cellular machinery.

Furthermore, applicant asserts that the methods used to block expression are not related to the ultimate function of the protein and therefore the only knowledge necessary would be the sequence of the protein or polymerase so that an appropriate site could be chosen. However, the instant specification does not describe such a broad genus of nucleic acid constructs that would conditionally control the expression of any polymerase or protein sequence based on the presence of any intron in any eukaryotic or prokaryotic cell. The specification does not disclose a structural characteristic that would allow one of ordinary skill to recognize which introns introduced into which sequences would result in expression or lack of expression of which polymerases or proteins.

Contrary to applicant's assertions, the specific example given in the specification is not representative of the broad genus of nucleic acid constructs that are instantly being claimed. The structural characteristics recited in the instant claims are extremely broad and the specification does not disclose a structural characteristic that would allow for the skilled artisan to envisage the entire genus claimed of nucleic acid constructs with any intron that would result in any polymerase to be incapable of being expressed

in any prokaryotic cells and capable of producing a nucleic acid sequence when introduced into any eukaryotic cell. Therefore, the skilled artisan would not be able to recognize that applicant was in possession of such a broad genus of nucleic acid constructs at the time of filing.

Applicant asserts that the Balvay et al. reference is better suited for a post-hoc explanation of why a particular site did not work rather than a predictive tool of why something is unlikely to work and that Balvay et al. only concerns itself with natural splice sites in natural genes. Contrary to applicant's assertions, the teachings of Balvay et al. are highly relevant to the breadth of the instant claims, as Balvay et al. discusses splicing machinery. Balvay et al. indicates that the splicing machinery is highly dependent upon recognizing and interacting with such secondary structures in making the splice. Balvay et al. indicates that the addition of a secondary structure to an existing mRNA can cause the cell to splice at a point not normally spliced at, while removal of such a structure can cause splicing to be eliminated (for example see pages 165 bridging to 166). Furthermore, Balvay indicates that the exon plays a significant role in splice site recognition by the cellular splicing machinery. Since one of skill would understand that the nucleotides in the exon remain in the mRNA (or ribozyme) after splicing, applicants claimed nucleic acid constructs, *following splicing*, would likely therefore contain elements of these exon recognition sites. Such unpredictability indicates that the genus of nucleic acid constructs comprising any intron in any polymerase (or any bacteriophage polymerase), or any toxic gene, and that are active or inactive depending on whether they are found in prokaryotic or eukaryotic cells is

very large.

Therefore, the teachings of the instant specification coupled with the breadth of the instant claims, is not considered to describe a representative sample of the genus of such constructs that would function as instantly recited.

Although applicant asserts that the examples that Balvay bring up are more in the nature of exceptions to the general rule and that there are normal rules of how and where splicing would occur and are predictable, these are simply assertions that are not supported by the instant specification or the art. The teachings of Balvay et al. support the unpredictability of the splicing mechanism, rather than the presence of common knowledge of the skilled artisan to the contrary, as asserted by applicant.

Claims 245-255, 258, 262 and 265 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. This rejection is repeated for the same reasons of record as set forth in the actions mailed 5/31/05, 6/27/06 and 4/4/07.

Applicant asserts that Example 19 provides a more than sufficient description regarding strategies used in choosing intron sequences to be used, insertion sites in the T7 polymerase and vectors, as well as construction steps. It is noted that the specific example in Example 19 is not commensurate in scope with the broadly recited characteristics of the nucleic acid constructs of the instant claims and does not

reasonably provide predictability of such a broad genus of nucleic acid constructs having the instantly desired function.

Applicant asserts that methods are well known in the art for introducing artificial introns. It is not disputed that methods are known in the art to introduce artificial introns. However, it is the unpredictable nature of introducing any intron into any nucleic acid sequence at any position that encodes any polymerase with a resultant incapability of the polymerase being expressed in any prokaryotic cell, whereas more than one copy of a nucleic acid sequence is produced when introduced into any eukaryotic cell. Furthermore, the claims recite that the gene product or protein expressed would be toxic specifically to a prokaryotic cell in the absence of the intron.

Applicants' specifically claim that the inserted and inactivating intronic sequences will be spliced out, a process the specification indicates will be carried out by the cellular machinery that normally operates to splice introns out of pre-mRNA sequences. Applicants indicate that such splicing restores native activity to previously inactive proteins. However, the specification as filed does not provide any nucleic acid constructs for which this has actually been shown to demonstrate the predictability of such a broad mechanism. Applicant's specification does not provide sufficient guidance or examples that would enable a skilled artisan to make the disclosed nucleic acid constructs containing sequences that are spliced out by cellular machinery without undue experimentation. Although the specification prophetically considers and discloses making and using such constructs, such a disclosure would not be considered enabling since introducing intervening sequences into nucleic acids alters

their secondary structure, which makes their ability to be cleaved by the splicing machinery unpredictable. The specification has not resolved such issues, since no exemplified constructs that contain intervening sequences and are inactive therefore, and by which later processing inside the cell restores activity. Applicants have simply not shown that such intervening sequences can be spliced out to restore any activity to previously inactive polymerases (or any toxic protein for that matter).

Applicant points to a statement of Balvay et al. "It is important to stress that in the absence of *in vivo* experiments or *in vitro* systems where transcription and splicing are coupled, all these conclusions about the functional significance of secondary structure should be taken as tentative ones." Although applicant interprets this statement as a tentative conclusion that is contrary to practical exercises that have been carried out generating *in vivo* data that introduction of introns into selected sites is a predictable art with a high likelihood of success, the statement of Balvay et al. actually supports the examiner's position. It is agreed that the issues of unpredictability due to secondary structure as taught by Balvay et al. could be overcome by *in vivo* experimentation, Balvay et al. is evidence that there are additional considerations such as secondary structure that would lead to unpredictability, absence evidence to the contrary. The instantly recited constructs have extremely broad structural characteristics that were not enabled by the instant specification or the state of the art at the time of filing.

Again, the issue is not whether it was known in the art how to insert introns, but rather how to insert introns in a predictable fashion in accordance with the breadth of the instant claims and have the desired outcome specific to eukaryotic and prokaryotic

cells with regards to any polymerase, as recited in the instant claims. Balvay et al. is simply an example that secondary structure is one complexity when considering splicing mechanisms.

In particular, it is demonstrated that the complex secondary structures of nucleic acids are responsible for their intron excision activity, and furthermore, that predicting the ability of the cellular splicing machinery to splice out precise intervening sequences from disrupted sequences with variable secondary structures such that native activity is restored is considered unpredictable, because the splicing machinery is sensitive to the presence or absence of such structures.

Applicant relies on Lewin for teachings regarding experiments of splicing out a hybrid intron and teachings that splicing sites are generic, meaning that they do not have specificity for individual RNA precursors and the RNA precursors do not convey specific information (such as secondary structure) that is needed for splicing. The teachings of Lewin et al. do not diminish the unpredictability of the intron splicing mechanism when a non-native intron is inserted into a sequence having secondary structure. Simply because splice sites are generic to different sequences that do not "convey" secondary structure that is needed for splicing does not mean that the mechanism does not encounter problems of unpredictability as taught by Balvay et al.

Furthermore, one of ordinary skill in the art would not be able to recognize which cells are "incompatible" or "compatible", as instantly recited, in view of the teachings of Lewin et al. that are cited by applicant. Specifically, if splicing sites are generic and do not have specificity for individual RNA precursors, as taught by Lewin et al., one would

not be able to determine without undue experimentation how such introns would get excised from some cells and not from others, as instantly recited. The instant nucleic acid construct has to be able to allow excision of the intron in some cells but not in others.

Furthermore, the replacement of even a few nucleotides on an mRNA can abolish all activity of the translated protein. It is maintained that neither the specification nor the prior art arms one of skill with the information necessary to engineer sequences into nucleic acid constructs that will be reliably spliced out to result in a protein with native activity restored.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would therefore require the *de novo* determination of intervening sequences that can be fully spliced out without leaving behind any nucleotides that might interfere with native activity. In the absence of sufficient guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

MPEP 2164.01

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention.

Also, MPEP 2164.01(a)

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

A conclusion of lack of enablement means that, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (see MPEP 2164.01(a)).

New Objections/Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 245-255, 258, 262 and 265 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Claim 245 has been amended to recite that the polymerase is "incapable of being expressed in a prokaryotic cell" due to the presence of the intron and that the polymerase is capable of producing more than one copy of a nucleic acid sequence from the construct when introduced into a "eukaryotic" cell.

Claim 255 has been amended to recite that the gene product is incapable of being expressed in a prokaryotic cell due to the presence of the intron and that the gene

product or protein expressed from the gene product would be toxic specifically to a prokaryotic cell in the absence of the intron.

Claim 262 has been amended to recite that the gene product is incapable of being expressed in a prokaryotic cell due to the presence of the intron, which in a eukaryotic cell is substantially removed during processing.

Each of these limitations constitutes new matter for the reasons explained below. Claims 246-254, 258, and 265 are rejected because they depend from claims 245, 255 or 262.

Applicant points to a passage on page 85 of the specification, as well as Example 19 and the description of Example 19 at page 89, for support for the instant amendments.

The passage on page 85 discloses that in a prokaryotic environment, the intron should remain in the mRNA as long as a self-splicing intron is not used. This teaching does not support the instant amendments requiring for the polymerase to be incapable of being expressed in a prokaryotic cell due to the presence of the intron and being capable of producing more than one copy of a nucleic acid sequence when introduced into a eukaryotic cell; does not support the instant limitation that the gene product is incapable of being expressed in a prokaryotic cell due to the presence of the intron, which in a eukaryotic cell is substantially removed during processing; and does not support the limitation that the gene product is incapable of being expressed in a prokaryotic cell due to the presence of the intron, which in a eukaryotic cell is substantially removed during processing. The passage on page 85 simply discloses

that it is possible that insertion of a heterologous processing element may not in all cases inactivate a gene when present in an "incompatible" cell and that in a prokaryotic environment, the intron should remain in the mRNA as long as a self-splicing intron is not used. However, the claims are not directed to whether or not self-splicing introns are utilized. Furthermore, simply because the specification discloses that non self-splicing introns should remain in the mRNA in a prokaryotic environment, this teaching is not support for each of the instant limitations discussed above.

Furthermore, Example 19 and the description of Example 19 at page 89 of the instant specification do not support the breadth of the instant limitations. Example 19 illustrates an example of the conditional activation of a gene by the precise introduction of an intron between the last two G's of a site that has the post splice junction sequence (C/A)AG, which is one example that is disclosed as being in hematopoietic cell lines, which are eukaryotic cells. This single example in a specific cell line with a construct with specific structural characteristics does not offer support for the broadly recited elements of the instant claims. This represents one species within a broad genus of nucleic acid constructs with broad structural features that are instantly claimed and not supported by the specification. The description of Example 19 discloses "Therefore, a construct with this modification could lack any expression of T7 RNA polymerase in an *E.coli* cell, but the normal coding sequence can be restored from transcripts after introduction into a compatible cell". Therefore, the specific example pointed to by applicant does not offer support for broad recitation of each of the structural characteristics of the nucleic acid construct discussed above and the specification does

not support such broad recitation of polymerases that are incapable of being expressed in any prokaryotic cells due to the presence of an intron and are capable of producing more than one copy of a nucleic acid sequence when introduced into any eukaryotic cell; and does not support resultant toxicity to prokaryotic cells in general in the absence of the intron.

There is no support for these claim limitations in the claimed priority document. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 11/25/1997, which is the filing date of the instant application.

A review of the specification does not reveal support for these claim amendments. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where specific support might exist for each claim limitation discussed above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1635

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